Synergistic gene-environment interactions increase schizophrenia risk

By Kristen Ryan

Using a novel genetically engineered mouse model, expressing a mutated form of the human disrupted in schizophrenia 1 (DISC1) gene, a risk factor for major psychiatric disorders, NIEHS-funded researchers investigated gene-environment interactions (GEI) that could act synergistically to contribute to mental illness.

Guilarte is also a member of the NIEHS National Advisory Environmental Health Sciences Council. (Photo courtesy of Steve McCaw)

Published May 28 in the journal Schizophrenia Bulletin, the new study *(http://www.ncbi.nlm.nih.gov/pubmed/23716713)* demonstrated that mice with mutated DISC1 (mDISC1) exposed to lead (Pb^{2+}) prenatally and throughout early life exhibited several neurobehavioral and neuroanatomical abnormalities that reflect human attributes of schizophrenia. Behavioral tests in these mice resulted in a sex-dependent increase in hyperactivity, alone and after treatment with psychostimulants.

The mice also had a mild impairment in their ability to adapt and suppress a startle response to loud noise, pointing to difficulties with attention and sensory information processing. Furthermore, magnetic resonance imaging (MRI) of these mice revealed enlarged lateral ventricles, or empty spaces filled with cerebrospinal fluid, in their brains. These findings were specific to lead-exposed mDISC1 mice, and were not observed in mutant mice on a control diet, or in normal DISC1 mice with or without lead exposure.

Lead senior author Tomas Guilarte, Ph.D., *(http://www.mailman.columbia.edu/our-faculty/profile?uni=trg2113)* an NIEHS-funded scientist and chair of the Department of Environmental Health Sciences at Columbia University Mailman School of Public Health, collaborated with first author Bagrat Abazyan, M.D., senior co-author Mikhail Pletnikov, M.D., Ph.D., and colleagues at Johns Hopkins University School of Medicine, to conduct this research study. The authors, who are well-established neuroscientists, wrote, "Our study is the first to use a relevant genetic mutation in combination with an environmental toxin implicated in schizophrenia in humans."

These findings have already been highlighted in several online reports, and the study continues to attract interest.

Extrapolating from gene-environment interactions in a mouse model

This research project was based on fundamental scientific premises generated by previous mechanistic and epidemiological studies that the authors reviewed.

- The glutamatergic hypothesis of schizophrenia, which implies a causal link between a decrease or hypoactivity of the N-methyl-d-aspartate receptor (NMDAR), located throughout the brain for control of synaptic plasticity and memory, and schizophrenia and other psychiatric disorders.
- The association of prenatal lead exposure with adult onset schizophrenia, based on its inhibitory action on NMDAR function.
- The involvement of GEI in schizophrenia and other mental disorders.

The GEI hypothesis is gaining attention and support, as the search continues for mutations in genes that could make individuals more or less susceptible to chemicals in the everyday environment. Earlier studies found the mutant form of DISC1 to be one those genes, and lead to be one of those chemicals, that affect NMDAR function.

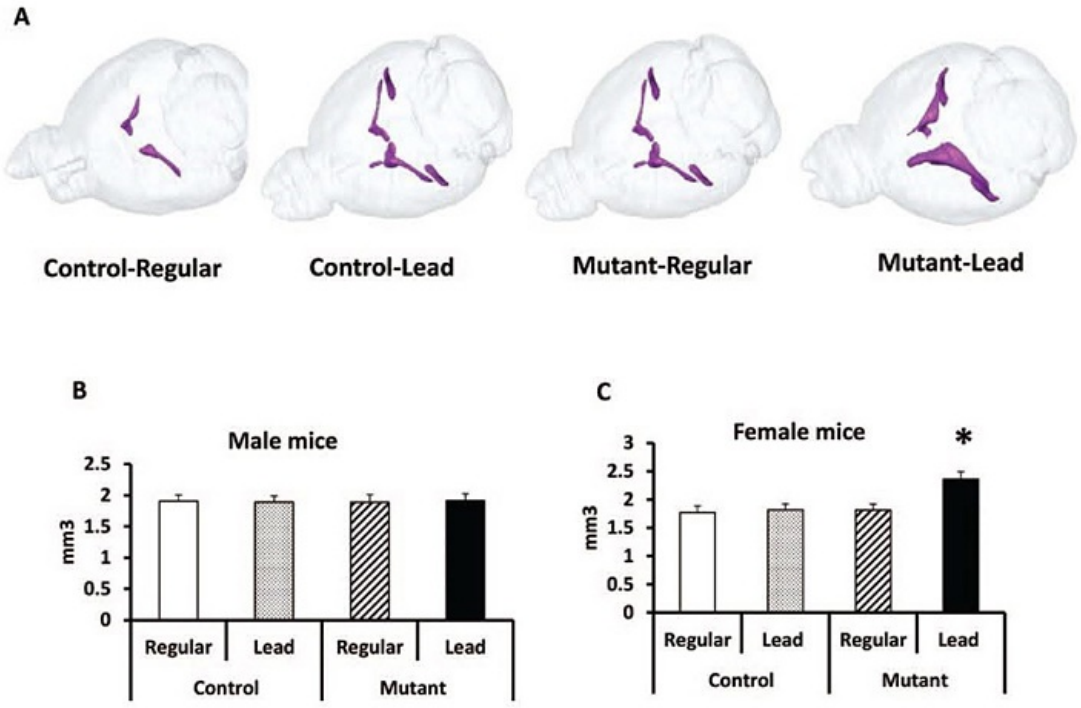
According to the researchers, this finding opens the door to possible combinations of gene-environment interactions that could contribute to the pathophysiology of numerous complex diseases. As Guilarte explained in an interview for a Columbia University press release, *(http://www.mailman.columbia.edu/news/lead-acts-trigger-schizophrenia)* "We're just scratching the surface. We used lead in this study, but there are other environmental toxins that disrupt the function of NMDAR. Similarly, any number of genes could be in play."

Notably, NIEHS and the National Toxicology Program are investigating the toxicity of various other chemical classes and mixtures, some of which are suspected to be risk factors for neurological disorders. Two examples are polycyclic aromatic hydrocarbons (PAHs) and flame retardants, both of which are widespread in the environment and have observed health effects. Ongoing and future research in genetically engineered rodent models, perhaps modeled after this study's model, could provide

greater insight into novel gene-environment interactions, and help explain some of the complex pathophysiology of mental illness and various other disorders.

Citation: Abazyan B, Dziedzic J, Hua K, Abazyan S, Yang C, Mori S, Pletnikov MV, Guilarte TR. *(http://www.ncbi.nlm.nih.gov/pubmed/23716713)*
2013. Chronic exposure of mutant DISC1 mice to lead produces sex-dependent abnormalities consistent with schizophrenia and related mental disorders: a gene-environment interaction study. Schizophr Bull; doi: 10.1093/schbul/sbt071 [Online 28 May 2013].

(Kristen Ryan, Ph.D., is an Intramural Research Training Award Fellow in the NTP Toxicology Branch.)



*In addition to molecular and behavioral studies, the team performed MRI studies of brain volume effects of gene-environment interaction. (A) Representative MRI 3D images for the control-regular, control-lead, mutant-regular, and mutant-lead groups of female mice, with the lateral ventricles are outlined in purple. (B) Male mice showed no genotype-related or diet-related alterations in lateral ventricle volume. (C) mDISC1 female mice exposed to Pb2+ had a marked increase in lateral ventricle volume compared with all other groups; *P = .05 for the genotype-diet interaction; n = 5 mice per group. (Photo courtesy of Tomas Guilarte)*

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